ETHYLENE OXIDE
(Group 1)

For definition of Groups, see Preamble Evaluation.

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Chem. Abstr. Name: Oxirane

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Ethylene oxide has been produced since the early 1900s, originally by the reaction of ethylene chlorohydrin with base and in recent years more commonly by catalytic oxidation of ethylene. It has been used as a chemical intermediate in the production of ethylene glycol, glycol ethers, nonionic surfactants and other industrial chemicals. Although much smaller amounts are used in sterilizing medical instruments and supplies in hospitals and industrially and for the fumigation of spices, it is during these uses that the highest occupational exposure levels have been measured.

5.2 Human carcinogenicity data

In epidemiological studies of exposure to ethylene oxide, the most frequently reported association has been with lymphatic and haematopoietic cancer. The populations studied fall into two groups - people using ethylene oxide as a sterilant and chemical workers manufacturing or using the compound. In general, people involved in sterilization are less likely to have occupational exposure to other chemicals.

Of the studies of sterilization personnel, the largest and most informative is that conducted in the USA. Overall, mortality from lymphatic and haematopoietic cancer was only marginally elevated, but a significant trend as found, especially for lymphatic leukaemia and non-Hodgkin's lymphoma, in relation to estimated cumulative exposure to ethylene oxide. For exposure at a level of 1 ppm [1.8 mg/m^3] over a working lifetime (45 years), a rate ratio of 1.2 was estimated for lymphatic and haematopoietic cancer. Three other studies of workers involved in sterilization (two in Sweden and one in the United Kingdom) each showed nonsignificant excesses of lymphatic and haematopoietic cancer.

In a study of chemical workers exposed to ethylene oxide at two plants in the USA, the mortality rate from lymphatic and haematopoietic cancer was elevated, but the excess was confined to a small subgroup with only occasional low-level exposure to ethylene oxide. Six other studies in the chemical industry (two in Sweden, one in the United Kingdom, one in Italy, one in the USA and one in Germany) were based on fewer deaths. Four found excesses of lymphatic and haematopoietic cancer (which were significant in two), and in two, the numbers of such tumours were as expected from control rates.

Because of the possibility of confounding occupational exposures, less weight can be given to the positive findings from the studies of chemical workers. Nevertheless, they are compatible with the small but consistent excesses of lymphatic and haematopoietic cancer found in the studies of

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sterilization personnel.

Some of the epidemiological studies of workers exposed to ethylene oxide show an increased risk for cancer of the stomach, which was significant only in one study from Sweden.

5.3 Animal carcinogenicity data

Ethylene oxide was tested for carcinogenicity in one experiment by oral administration in rats, in two experiments by inhalation in mice and two experiments by inhalation in rats. It was also tested in single studies in mice by skin application and by subcutaneous injection.

In the experiment by intragastric intubation in rats, ethylene oxide produced tumours of the forestomach, which were mainly squamous-cell carcinomas. In one study in mice, inhalation of ethylene oxide resulted in increased incidences of alveolar/bronchiolar lung tumours and tumours of the Harderian gland in animals of each sex and of uterine adenocarcinomas, mammary carcinomas and malignant lymphomas in females. In a bioassay of pulmonary tumours in strain A mice, inhalation of ethylene oxide increased the number of pulmonary adenomas per mouse. In the two experiments in which rats of one strain were exposed by inhalation, ethylene oxide increased the incidences of mononuclear-cell leukaemia and brain tumours in animals of each sex and of peritoneal mesotheliomas in the region of the testis and subcutaneous fibromas in males. Ethylene oxide produced local sarcomas in mice following subcutaneous injection. In a limited study in mice treated by skin application, no skin tumours were observed.

5.4 Other relevant data

Inhaled ethylene oxide is readily taken up in man and rat, and aqueous ethylene oxide solutions can penetrate human skin. Ethylene oxide is uniformly distributed throughout the body of rats. Its half-life has been estimated as between 14 min and 3.3 h in the human body and about 6 min in rats. Exposure of rats to 5 ppm [9 mg/m^3] resulted in steady-state ethylene oxide levels in blood of 60 ng/g. Whole-body elimination of ethylene oxide from rats is described by first-order kinetics. It is excreted mainly in the urine as thioethers; at high doses, the proportion of thioethers is reduced, while the proportion of ethylene glycol increases. Rats conjugate ethylene oxide with glutathione to a greater extent than mice, while rabbits do not appear to be capable of this reaction.

Ethylene oxide was not teratogenic to rats or rabbits exposed by inhalation to concentrations up to 150 ppm [270 mg/m^3]. It was teratogenic to mice after intravenous injection in a single study. Surprisingly, brief exposure of dams around the time of fertilization to a high concentration (1200 ppm [2160 mg/m^3]) of ethylene oxide by inhalation induced teratogenic effects in mice. The effect was shown to be due to a direct action on the zygote.

Ethylene oxide forms adducts with proteins in both man and experimental animals and with DNA in experimental animals. Haemoglobin adducts have been used for biomonitoring, as there is a significant correlation between cumulative exposure over four months and levels of N-terminal hydroxyethyl valine in haemoglobin of exposed workers. The increment of hydroxyethyl valine adduct formed is about 3.5 pmol/g haemoglobin per ppm-h ethylene oxide. Higher proportions of hydroxyethyl histidine are formed. Hydroxyethyl haemoglobin adducts are also found in the absence of known exposure to ethylene oxide. Greater numbers of haemoglobin and DNA adducts occur per unit of exposure in rats and mice at high concentrations (> 33 ppm) than at lower concentrations. 7-Hydroxyethylguanine is quantitatively the most important DNA adduct formed. Its half-life varies

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from 1.0 to 6.9 days in mouse and rat tissues.

Studies of workers exposed to ethylene oxide in hospital and factory sterilization units and in ethylene oxide manufacturing and processing plants consistently showed chromosomal damage in peripheral blood lymphocytes, including chromosomal aberrations in 11 of 14 studies, sister chromatid exchange in 20 of 23 studies, micronuclei in three of eight studies and gene mutation in one study. Micronuclei were induced in the bone marrow of exposed workers in one study. In general, the degree of damage is correlated with level and duration of exposure. The induction of sister chromatid exchange appears to be more sensitive to exposure to ethylene oxide than is that of either chromosomal aberrations or micronuclei. In one study, chromosomal aberrations were observed in the peripheral lymphocytes of workers two years after cessation of exposure to ethylene oxide, and sister chromatid exchanges six months after cessation of exposure.

Chromosomal aberrations and sister chromatid exchange were induced in cynomolgus monkeys exposed to ethylene oxide. Ethylene oxide also induced gene mutation, specific locus mutation, sister chromatid exchange, chromosomal aberrations, micronuclei, dominant lethal mutation and heritable translocation in rodents treated *in vivo*. It induced unscheduled DNA synthesis, gene mutation, sister chromatid exchange and chromosomal aberrations in human cells and gene mutation, micronuclei, chromosomal aberrations and cell transformation in rodent cells *in vitro*.

Analogous genetic and related effects were observed in nonmammalian systems.

5.5 Evaluation

There is *limited evidence* in humans for the carcinogenicity of ethylene oxide.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethylene oxide.

In making the overall evaluation, the Working Group took into consideration the following supporting evidence. Ethylene oxide is a directly acting alkylating agent that:

(i) induces a sensitive, persistent dose-related increase in the frequency of chromosomal aberrations and sister chromatid exchange in peripheral lymphocytes and micronuclei in bone-marrow cells of exposed workers;

(ii) has been associated with malignancies of the lymphatic and haematopoietic system in both humans and experimental animals;

(iii) induces a dose-related increase in the frequency of haemoglobin adducts in exposed humans and dose-related increases in the numbers of adducts in both DNA and haemoglobin in exposed rodents;

(iv) induces gene mutations and heritable translocations in germ cells of exposed rodents; and

(v) is a powerful mutagen and clastogen at all phylogenetic levels.

Overall evaluation

Ethylene oxide is *carcinogenic to humans (Group 1)*.

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For definition of the italicized terms, see Preamble Evaluation.

Previous evaluation: Suppl. 7 (1987) (p. 205)

Synonyms

- Dihydrooxirene
- Dimethylene oxide
- 1,2-Epoxyethane
- Epoxyethane
- Ethene oxide
- EtO
- ETO
- Oxacyclopropane
- Oxane
- Oxidoethane

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